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Application No.: 09/644,668
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PATENT

the above named sequences, SEQ I NOS:1-41, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disc.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

The sequence identified in the instant application as SEQ ID NO:1 was inadvertently omitted from the application but was incorporated by reference to priority application 60/150,452, filed August 24, 1999. Thus, Applicants believe that entry of the sequence into the instant application does not constitute new matter.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning on page 7, line 7, has been amended as follows:

Some human sequence antibodies of the invention comprise heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO:27), FISYDGSNKHYADSVKG (SEQ ID NO:33) and TGWLGPFDY (SEQ ID NO:[38]37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO:25), GASSRAT (SEQ ID NO:30), and QQYGSSPWT (SEQ ID NO:35), respectively.

The paragraph beginning on page 7, line 13, has been amended as follows:

Other human sequence antibodies of the invention comprise heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO:28), VIWYDGSNKYYADSVKG (SEQ ID NO:34) and APNYIGAFDV (SEQ ID NO:[39]38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO:26), AASSLQS (SEQ ID NO:31), and QQYNSYPPT (SEQ ID NO:36), respectively.

The paragraph beginning on page 8, line 3, has been amended as follows:

The invention provides a hybridoma cell line comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human sequence heavy chain transgene and a human sequence light chain transgene, wherein the hybridoma produces a human sequence antibody that specifically binds to human CTLA-4. In a related embodiment, the hybridoma secretes a human sequence antibody that specifically binds human CTLA-4 or binding fragment thereof, wherein the antibody is selected from the group consisting of: a human sequence antibody comprising heavy chain heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH

(SEQ ID NO:27), FISYDGNNKYYADSVKG (SEQ ID NO:32) and TGWLGPFDY (SEQ ID NO:37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVGSSYLA (SEQ ID NO:24), GAFSRAT (SEQ ID NO:29), and QQYGSSPWT (SEQ ID NO:35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:17 and SEQ ID NO:7, respectively; a human sequence antibody comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO:27), FISYDGNSNKHYADSVKG (SEQ ID NO:33) and TGWLGPFDY (SEQ ID NO:[38]37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO:25), GASSRAT (SEQ ID NO:30), and QQYGSSPWT (SEQ ID NO:35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:19 and SEQ ID NO:9, respectively; or a human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO:28), VIWYDGNSNKYYADSVKG (SEQ ID NO:34) and APNYIGAFDV (SEQ ID NO:[39]38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO:26), AASSLQS (SEQ ID NO:31), and QQYNSYPPT (SEQ ID NO:36), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:23 and SEQ ID NO:13, respectively.

Table 3, on page 74, lines 1-4, has been amended as follows:

Chain	HuMAb	CDR1	SEQ ID NO:	CDR2	SEQ ID NO:	CDR3	SEQ ID NO:
Light Chain	10D1 4B6 1E2	RASQSVGSSYLA RASQSVSSSFLA RASQGISSWLA	24 25 26	GAFSRAT GASSRAT AASSLQS	29 30 31	QQYGSSPWT QQYGSSPWT QQYNSYPPT	35 35 36
Heavy Chain	10D1 4B6 1E2	SYTMH SYTMH SYGMH	27 27 28	FISYDGNNKYYADSVKG FISYDGNSNKHYADSVKG VIWYDGNSNKYYADSVKG	32 33 34	TGWLGPFDY TGWLGPFDY APNYIGAFDV	37 [38]37 [38]38

The paragraph beginning on page 76, line 16, has been amended as follows:

The kappa light chain plasmid, pCK7-96 (SEQ ID NO:[40]39), includes the kappa constant region and polyadenylation site, such that kappa sequences amplified with 5' primers that include HindIII sites upstream of the initiator methionine can be digested with HindIII and BbsI, and cloned into pCK7-96 digested with HindIII and BbsI to reconstruct a complete light chain coding sequence together with a polyadenylation site. This cassette can be isolated as a HindIII/NotI fragment and ligated to transcription promoter sequences to create a functional minigene for transfection into cells.

The paragraph beginning on page 76, line 23, has been amended as follows:

The gamma1 heavy chain plasmid, pCG7-96 (SEQ ID NO:[41]40), includes the human gamma1 constant region and polyadenylation site, such that gamma sequences amplified with 5' primers that include HindIII sites upstream of the initiator methionine can be digested with HindIII and AgeI, and cloned into pCG7-96 digested with HindIII and AgeI to reconstruct a complete gamma1 heavy chain coding sequence together with a polyadenylation site. This cassette can be isolated as a HindIII/SalI fragment and ligated to transcription promoter sequences to create a functional minigene for transfection into cells.

The paragraph beginning on page 76, line 31, has been amended as follows:

The gamma4 heavy chain plasmid, pG4HE (SEQ ID NO:[42]41), includes the human gamma4 constant region and polyadenylation site, such that gamma sequences amplified with 5' primers that include HindIII sites upstream of the initiator methionine can be digested with HindIII and AgeI, and cloned into pG4HE digested with HindIII and AgeI to reconstruct a complete gamma4 heavy chain coding sequence together with a polyadenylation site. This cassette can be isolated as a HindIII/EcoRI fragment and ligated to transcription promoter sequences to create a functional minigene for transfection into cells.

The following new paragraph has been inserted immediately before the paragraph beginning on page 93, line 1, of the specification:

SEQ ID NO:1 pGP1k

AATTAGCGGC CGCTGTCGAC AAGCTTCGAA TTCAGTATCG ATGTGGGGTA	50
CCTACTGTCC CGGGATTGCG GATCCCGAT GATATCGTTG ATCCTCGAGT	100
GCGGCCGCAAG TATGCAAAAA AAAGCCCGCT CATTAGGCAG GCTCTTGGCA	150
GAACATATCC ATCGCGTCCG CCATCTCCAG CAGCCGCACG CGGCGCATCT	200
CGGGCAGCGT TGGGTCTTGG CCACGGGTGC GCATGATCGT GCTCTGTGCG	250
TTGAGGACCC GGCTAGGCTG GCGGGGTTGC CTTACTGGTT AGCAGAACGAA	300
ATCACCGATA CGCGAGCGAA CGTGAAGCGA CTGCTGCTGC AAAACGTCTG	350
CGACCTGAGC AACAAACATGA ATGGTCTTCG GTTTCCGTGT TTCGTAAGT	400
CTGGAAACGC GGAAGTCAGC GCCCTGCACC ATTATGTTCC GGATCTGCAT	450
CGCAGGATGC TGCTGGCTAC CCTGTGGAAC ACCTACATCT GTATTAACGAA	500
AGCGCTGGCA TTGACCCCTGA GTGATTTTC TCTGGTCCCG CCGCATCCAT	550
ACCGCCAGTT GTTACCCCTC ACAACGTTCC AGTAACCGGG CATGTTCATC	600
ATCAGTAACC CGTATCGTGA GCATCCTCTC TCGTTTCATC GGTATCATTAA	650
CCCCCATGAA CAGAAATTCC CCCTTACACG GAGGCATCAA GTGACCAAAC	700
AGGAAAAAAAC CGCCCTTAAC ATGGCCCGCT TTATCAGAAC CCAGACATTA	750
ACGCTTCTGG AGAAACTCAA CGAGCTGGAC CGGGATGAAC AGGCAGACAT	800
CTGTGAATCG CTTCACGACC ACGCTGATGA GTCTTACCGC AGCTGCCTCG	850
CGCGTTTCGG TGATGACGGT GAAAACCTCT GACACATGCA GCTCCCGGAG	900
ACGGTCACAG CTTGTCTGTA AGCGGATGCC GGGAGCAGAC AAGCCCGTCA	950
GGGCGCGTCA CGGGGTGTTG CGGGGTGTCG GGGCGCAGCC ATGACCCAGT	1000
CACGTAGCGA TAGCGGAGTG TAACTATGCG GCATCAGAGC	1050
AGATTGTACT GAGAGTGCAC CATATCGGGT GTGAAATACC GCACAGATGC	1100
GTAAGGAGAA AATACCGCAT CAGGGCCTCT TCCGCTTCC CGCTCACTGA	1150
CTCGCTGCGC TCGGTCGTT GGCTGCGCG AGCGGTATCA GCTCACTCAA	1200
AGGCAGTAAT ACGGTTATCC ACAGAACAGG GGGATAACGC AGGAAAGAAC	1250
ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA AGGCCCGT	1300
GCTGGCGTT TTCCATAGGC TCCGCCCGG TGACGAGCAT CACAAAAATC	1350
GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAAG	1400
GCGTTTCCCC CTGGAAGCTC CCTCGTGCAG TCTCCTGTT CGACCCCTGCC	1450
GCTTACCGGA TACCTGTCCG CCTTTCTCCC TTGGGAAGC GTGGCGCTTT	1500
CTCATAGCTC ACGCTGTAGG TATCTCAGTT CGGTGTAGGT CGTCGCTCC	1550
AAGCTGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC GCTGCGCCTT	1600
ATCCGTAAC TATCGTCTTG AGTCCAACCC GTAAAGACAC GACTTATCGC	1650
CACTGGCAGC AGCCAGGCAGC GCCTTGGCCT AAGAGGCCAC TGGTAACAGG	1700
ATTAGCAGAG CGAGGTATGT AGGCAGGTGCT ACAGAGTTCT TGAAGTGGTG	1750
GCCTAACTAC GGCTACACTA GAAGGACAGT ATTTGGTATC TGGCTCTGC	1800
TGAAGCCAGT TACCTTCGGA AAAAGAGTTG GTAGCTCTTG ATCCGGCAAA	1850
CAAACCACCG CTGGTAGCGG TGGTTTTTT GTTGCAAGC AGCAGATTAC	1900
GCGCAGAAAA AAAGGATCTC AAGAACATCC TTGATCTT TCTACGGGGT	1950
CTGACGCTCA GTGGAACGAA AACTCACGTT AAGGGATTT GGTATGAGA	2000
TTATCAAAAA GGATCTTCAC CTAGATCCIT TTAAATTAAA AATGAAGTTT	2050
TAAATCAATC TAAAGTATAT ATGAGTAAAC TTGGTCTGAC AGTTACCAAT	2100
GCTTAATCAG TGAGGCACCT ATCTCAGCGA TCTGTCATT CGTTCATCC	2150
ATAGTTGCCT GACTCCCCGT CGTGTAGATA ACTACGATAC GGGAGGGCTT	2200
ACCATCTGGC CCCAGTGCTG CAATGATACC GCGAGACCCA CGCTCACCGG	2250
CTCCAGATT ATCAGCAATA AACCAAGCCAG CGGAAGGGC CGAGCGCAGA	2300
AGTGGTCCTG CAACTTATC CGCCTCCATC CAGTCTATTA ATTGTTGCCG	2350
GGAAGCTAGA GTAAGTAGTT CGCCAGTTAA TAGTTGCGC AACGTTGTTG	2400
CCATTGCTGC AGGCATCGTG GTGTCAAGCT CGTCGTTGG TATGGCTTCA	2450
TTCAAGCTCCG GTTCCCAACG ATCAAGGCAG GTTACATGAT CCCCCATGTT	2500

GTGCAAAAAA GCGGTTAGCT CCTTCGGTCC TCCGATCGTT GTCAGAAGTA	2550
AGTTGGCCCG AGTGTATCA CTCATGGTTA TGGCAGCACT GCATAATTCT	2600
CTTACTGTCA TGCCATCCGT AAGATGCTTT TCTGTGACTG GTGAGTACTC	2650
AACCAAGTCA TTCTGAGAAT AGTGTATGCG GCGACCGAGT TGCTCTTGCC	2700
CGGCGTCAAC ACGGGATAAT ACCCGGCCAC ATAGCAGAAC TTTAAAAGTG	2750
CTCATCATTG GAAAACGTTT TTGGGGCGA AAACTCTCAA GGATCTTACC	2800
GCTGTTGAGA TCCAGTCGA TGTAAACCCAC TCGTGCACCC AACTGATCTT	2850
CAGCATCTT TACTTCACC AGCGTTCTG GGTGAGCAAA AACAGGAAGG	2900
CAAAATGCCG CAAAAAAGGG AATAAGGGCG ACACGGAAAT GTTGAATACT	2950
CATACTCTTC CTTTTCAAT ATTATTGAAG CATTATCAG GGTTATTGTC	3000
TCATGAGCGG ATACATATTG GAATGTATTG AGAAAAATAA ACAAAATAGGG	3050
GTTCGCGCA CATTCCCCG AAAAGTGCCA CCTGACGTCT AAGAAACCAT	3100
TATTATCATG ACATTAACCT ATAAAAATAG GCGTATCACG AGGCCCTTTC	3150
GTCTTCAAG	3159

The paragraph beginning on page 93, line 1, has been amended as follows:

pCK7-96 (Nucleotide residues 3376 to 3881)(SEQ ID NO:39)

AGGAGAATGAATAAATAAAAGTGAATCTTGCACCTGTGGTTCTCTCTTCCCAATTAAATAATTATT
ATCTGTTGTTACCAACTACTCAATTCTCTTATAAGGGACTAAATATGTAGTCATCTTAAGGCGCATA
ACCATTATAAAAATCATCCTTCATTCTATTTACCCATCATCCTCTGCAAGACAGTCCTCCCTCAA
CCACAAGCCTCTGCTCACAGTCCCCTGGGCCATGGATCCTCACATCCAATCCGCGGCCGCAATT
CGTAATCATGGTCATAGCTGTTCTGTGTGAAATTGTTATCCGCTCACATTCCACACAATACGAG
CCGGAAGCATAAAGTGTAAAGCCTGGGTGCTAATGAGTGAGCTAACTCACATTAAATTGCGTTGCGCT
CACTGCCCGTTCCAGTCGGAAACCTGTCGTGCCAGCTGCATTAATGAATCGGCCAACGCGCGGGGA
GAGGCGGTTGCGTATTGGCGC

The paragraph beginning on page 93, line 8, has been amended as follows:

pCG7-96 (SEQ ID NO:[41]40)

The paragraph beginning on page 94, line 12, has been amended as follows:

pG4HE (SEQ ID NO:[42]41)

The paragraph beginning on page 95, line 17, has been amended as follows:

10D1 VH(SEQ ID NO:16)

The paragraph beginning on page 95, line 27, has been amended as follows:

10D1 VK(SEQ ID NO:6)

The paragraph beginning on page 95, line 37, has been amended as follows:

4B6 VH(SEQ ID NO:18)

The paragraph beginning on page 95, line 47, has been amended as follows:

4B6 VK(SEQ ID NO:8)

The paragraph beginning on page 95, line 57, has been amended as follows:

1E2 VH(SEQ ID NO:22)

The paragraph beginning on page 96, line 7, has been amended as follows:

1E2 VK(SEQ ID NO:12)

IN THE CLAIMS:

31. (Amended) The human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO:27), FISYDGSNKHYADSVKG (SEQ ID NO:33) and TGWLGPFDY (SEQ ID NO:[38]37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO:25), GASSRAT (SEQ ID NO:30), and QQYGSSPWT (SEQ ID NO:35), respectively.

32. (Amended) The human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO:28), VIWYDGSNKYYADSVKG (SEQ ID NO:34) and APNYIGAFDV (SEQ

ID NO:[39]38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO:26), AASSLQS (SEQ ID NO:31), and QQYNSYPPT (SEQ ID NO:36), respectively.

Claim 46. (Amended) A hybridoma secreting a human sequence antibody that specifically binds human CTLA-4 or binding fragment thereof, wherein the antibody is selected from the group consisting of:

a human sequence antibody comprising heavy chain heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO:27), FISYDGNNKYYADSVKG (SEQ ID NO:32) and TGWLGPFDY (SEQ ID NO:37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVGSSYLA (SEQ ID NO:24), GAFSRAT (SEQ ID NO:29), and QQYGSSPWT (SEQ ID NO:35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:17 and SEQ ID NO:7, respectively,

a human sequence antibody comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYTMH (SEQ ID NO:27), FISYDGGSNKHYADSVKG (SEQ ID NO:33) and TGWLGPFDY (SEQ ID NO:[38]37), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQSVSSSFLA (SEQ ID NO:25), GASSRAT (SEQ ID NO:30), and QQYGSSPWT (SEQ ID NO:35), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:19 and SEQ ID NO:9, respectively, and

a human sequence antibody of claim 1, comprising heavy chain CDR1, CDR2, and CDR3 sequences, SYGMH (SEQ ID NO:28), VIWYDGGSNKYYADSVKG (SEQ ID NO:34) and APNYIGAFDV (SEQ ID NO:[39]38), respectively, and light chain CDR1, CDR2, and CDR3 sequences, RASQGISSWLA (SEQ ID NO:26), AASSLQS (SEQ ID NO:31), and QQYNSYPPT (SEQ ID NO:36), respectively, and heavy chain and light chain variable region amino acid sequences as set forth in SEQ ID NO:23 and SEQ ID NO:13, respectively.